Zabdiel Boylston's evaluation of inoculation against smallpox

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Variolation, known in the 18th century as inoculation, was introduced almost simultaneously in Boston and London in the early 1720s.[1] A furious debate followed. Among the issues were the religious implications of interfering with divine providence; the legality of spreading a potentially fatal infection; whether the disease induced really was smallpox; whether it was safer than natural smallpox; and whether inoculation induced immunity. Thomas Nettleton, a Yorkshire physician and inoculator, suggested in a letter sent in 1722 to James Jurin, Secretary of the Royal Society, that the best way to answer the safety and efficacy question was to make a comparison between the mortality of smallpox and the mortality among those inoculated.[2,3] He submitted 3405 cases of natural smallpox, of which 636 died, whereas there had been no deaths among the 60 patients he had inoculated.

Jurin took up the suggestion and advertised for information from anyone with experience of natural smallpox or variolation.[4] To simplify the investigation and avoid arguments about subjective issues such as the severity of an individual case he only recorded death or survival. His correspondents revealed that the operation was practised throughout England and that the operators ranged from fully licensed physicians to surgeons, apothecaries and lay women.[5] Jurin published annual summaries of his correspondence between 1724 and 1727.[6–10]

Table 1 shows the data presented by Boylston[13] and Jurin,[9] analysed using a simple χ^2 analysis. The mortality among inoculees was similar on both sides of the Atlantic, but while natural smallpox was associated with a higher death rate than inoculation in both places, the relative increase in the rate was 8 in Boston and 6.9 in England. This apparently similar effectiveness was present despite differences in the operators and the exact method of inoculation.

This very early use of mathematical evidence in favour of inoculated smallpox over the natural disease influenced the adoption of variolation both in England and in the colonies. In 1731 David Hartley, now remembered as the father of psychology,[14] used these figures to argue for general inoculation in the town of Bury St Edmunds because it would save about 600 lives.[15] In 1730, when smallpox reappeared in Boston, Boylston republished his book and several of the town's doctors, including William Douglass, his old nemesis, now offered variolation to their patients.[16]

The published evidence was taken so seriously that opponents of variolation tried to argue that the figures were biased.[4,17] They complained that inoculators regularly excluded pregnant women and those in ill health, and that they were treating a healthier population than those who suffered the natural disease. The title of Boylston's book – *An historical account of the smallpox inoculated in New England upon all sorts of persons, whites, blacks, and of all ages and constitution* – may represent a reply to these criticisms. The efficacy and relative safety of inoculation compared with natural disease was accepted both in England and in the North American colonies. It was used in Philadelphia in 1735 and Charleston, South Carolina in 1738 when epidemic smallpox appeared. By the middle of the 18th century John Adams and Thomas Jefferson

Table 1
Fatality of natural and inoculated smallpox

	Boston[*]		*England*[†]	
	Died	Survived	Died	Survived
Natural smallpox	844	4915	2848	19303
Inoculated smallpox	6	276	13	611[‡]

[*] Relative risk natural vs inoculated smallpox: 6.9 (range 3.2–15) p <.0011
[†] Relative risk natural vs inoculated smallpox: 8.0 (range 4.7–13.6) p <.0011
[‡] Relative risk inoculated in Boston vs England: 1.02 (range 0.4–2.6) p >.9

had been inoculated and the Royal College of Physicians had endorsed the practice as safe and beneficial.[4,18]

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